UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/378,046	08/20/1999	JOHN MANFREDI	CPI-088	8652

959 7590 04/08/2002

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	14

DATE MAILED: 04/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/378,046	Manfredi et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 26, 2002*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-41 and 43-52* is/are pending in the applica

4a) Of the above, claim(s) *3, 10-13, 17-22, 44, and 45* is/are withdrawn from considera

5) ☒ Claim(s) *51* is/are allowed.

6) ☒ Claim(s) *1, 2, 4-9, 14-16, 23-41, 43, 46-50, and 52* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jan 26, 2002* is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Claims 1-50 and new claims 51 and 52 are pending.

2. Applicant is notified that the amendments put forth in Paper 12, 1/24/02, have been entered in full.

3. Claims 3, 10-13, 17-22, and 44-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of the invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

4. As per the restriction requirement of Paper 8, 2/20/01, Applicant was required to elect for prosecution on the merits a single disclosed species of the instant invention, i.e. the embodiment of a single cell type - such embodiment consisting of only those components which could or would be present together in one cell and which would function together in one particular cell. Accordingly, Applicant elected for prosecution on the merits a yeast cell comprising an STE2 G-protein coupled receptor, a FUS1-LacZ reporter construct, a FUS1-STE5 construct which may or may not have contain a hypersensitive STE5 mutation. Further, the elected yeast cell may or may not have a mutation in the endogenous STE5 gene. Additionally, the STE2 G-protein coupled receptor may be endogenous to the yeast cell or heterologously expressed in the yeast cell. Further, the elected yeast cell may have a mutation in a gene, which gene negatively regulates the pheromone response.

The examiner finds that claims 1, 2, 4-9, 14-16, 23-41, 43 and 46-52 read on this elected species. Applicant, again, traverses the restriction requirement for allegedly being improper. Applicant argues that the pending claims represent an intricate web of knowledge, continuity of effort, and consequences of a single invention, which merit examination of all embodiments of the invention, particularly as the claims relate to yeast cells and more particularly as these claims relate to genes involved in the yeast pheromone receptor pathway. This argument has been fully considered but not deemed persuasive as set forth previously. A search of the claimed invention is not limited to that which might anticipate the instant invention but also to that which might render the invention obvious. A report of assay systems encompassed by the pending claims could be present the literature of practically any area of molecular biology; such a report might either anticipate or render the claims obvious, and as such, a search of the entire field of molecular biology would be unduly burdensome. Therefore, the restriction requirement is maintained and made final.

Drawings

5. The corrected or substitute drawings were received on 1/26/02. These drawings are not acceptable because they appear to have been damaged by irradiation of the mail. Applicant is required to submit new drawings. Applicant is reminded that a reply to this office action, to be complete, must include such drawings.

Withdrawn Rejections:

6. The rejection of claim 41 under 35 U.S.C. 102(a) and (e) as being anticipated by U.S. Patent No: 5691188 is withdrawn in view of Applicants' amendments put forth in 12.

Maintained Rejections:

7. Claims 1, 2, 4-9, 14-16, 23-40, 46-50 and 52 are rejected under 35 U.S.C. 112, first paragraph, as set forth previously in Paper 11, 6/6/01, and reiterated below:

The specification, while being enabling for a yeast cell comprising a G-protein coupled receptor, a FUS1-LacZ reporter construct, a FUS1-STE5 construct wherein the STE5 does not contain a hypersensitive mutation, does not reasonably provide enablement for a cell comprising a heterologous DNA construct comprising a gene encoding a protein that activates a signal transduction pathway, which gene is operably linked to a promoter that is responsive to activation of the signal transduction pathway, wherein said gene in not STE5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant is claiming a genus of assay systems that rely on a positive feedback loop occurring within a signal transduction cascade, such that the signal generated from ligand binding to a receptor is amplified via the positive feedback loop. Applicant has disclosed a single working example of this genus as Example 1 (page 66 and Figures 1 and 2), wherein the FUS1 promoter drives the expression of STE5 in response to the activation of a heterologously

expressed C5a receptor. The claims encompass a practically limitless number of potential assays systems wherein different components of the yeast pheromone response signal transduction cascade are mixed and matched such that a positive feedback loop is established by at least one of the members of the cascade. However, the specification provides merely an invitation to the skilled artisan to try and find those components which might ultimately work together and also to try to find the correct expression systems, e.g. high or low copy plasmids, to get those components to work together.

One of skill in the art of intracellular signal transduction appreciates that this field is extremely complex, and, as the transduction components are often in a delicate balance with each other, these systems are also extremely unpredictable. It is simply beyond the skill of one highly skilled in the art to predict what the effect of the introduction of a positive feedback loop into one of these systems will have, e.g. rate limiting factors can be titrated out of the cascade or constitutive saturation of the response can occur due to high basal expression of any members of the cascade. For example, the specification contemplates the use of the cyclase responsive element binding protein (CREB) (see page 58) which is known to be a component of many G-protein activated signal transduction cascades including MAP Kinase cascades. CREB activates target gene expression by binding to cyclase responsive element (CRE) sequences in the promoters of target genes. Francis J. et al. (Society for Neuroscience Abstracts 26(1-2) abs.. No. 49.16, 2000) report the results of an assay system that is encompassed by the instant claims, wherein a CRE-luciferase porter plasmid was induced by okadiac acid. Surprisingly,

cotransfection with a CRE-CREB expression cassette significancy *reduced* the okadiac acid associated induction of luciferase expression. This result would not be expected based on the model taught in the instant specification because the positive feedback from the CRE-CREB construct should have amplified the luciferase response.

Applicant has presented results using FUS1-STE5. On face value, such a construct would not be expected to either cause constitutive activation of the response or diminished response due to the titration of rate limiting factors. As set forth in the specification, STE5 is thought to provide a scaffolding for the recruitment of the G-protein βγ subunits and the downstream kinases. Overexpession of STE5 is not known to cause high level constitutive activation of the mating response or to bypass the need for G-protein βγ subunits (see page 1061 col. 1 of Hasson et al., Mol. Cell. Biol. 14(2)1054-1056, 1994). Claims 14-16 and 33 require that the STE5 be a hypersensitive mutant which is known to cause high level constitutive activation of the mating response. Hasson et al. teach that the STE5 hypersensitive mutant "appears to be qualitatively different" from STE5 because it bypasses the need for G-protein βγ subunits and results in a 100 fold increase in transcription of the reporter gene (see page 1061 col. 1 of Hasson et al). The FUS1 promoter is known to have a strong basal activity (see Table 3, page 2958 of Hagen et al. Mol. Cell. Biol. 11(6)2952-2961, 1991). Thus, one could only guess at what the effect might be of putting the hypersensitive STE5 mutant in control of its own production, as is required of claims 14-16 and 33. Absent evidence to the contrary, the expectation is that the basal transcription of the hypersensitive STE5 mutant coupled to the positive feedback loop

would lead to rapid constitutive activation of the cascade, and thus would defeat the proposed use of the assay. This expectation is also true of the claimed FUS1-STE4 construct. Like the hypersensitive STE5 mutant, STE4 overexpression results in constitutive activation of the cascade (see page 105-1055 of Hasson et al.) and would also be expected to lead to constitutive activation of the cascade when its expression is controlled by the FUS1 promoter. The specification has merely presented the skilled artisan with an invitation to try these experiments and perhaps to try to find a way to regulate or fine tune the expression of STE4 or the hypersensitive STE5 mutant in such a way that the assay would work, if that is indeed possible.

Therefore, due to the large quantity of experimentation required of the skilled artisan to try and find other transduction components, besides STE5, that would work in the assay as claimed, and to try to find ways in which to control their levels of expression, the lack of working examples other than that of STE5, the lack of guidance in the specification other than a mere invitation to the skilled artisan to begin to try the proposed experiments, the complex and contradictory state of the prior art that indicates that the effect of a positive feedback loop inserted into a signal transduction cascade cannot be predicted (see Francis et al. above), undue experimentation would be required of the skilled artisan to make and use the invention commensurate in scope with the claims.

Applicant argues that the skill level in the area of recombinant cells having amplified signal transduction pathway responses is quite high and, and that the area of technology is relatively predicable. This argument has been fully considered but not deemed persuasive.

While it maybe true that the skill level in the area of amplified signal transduction pathway responses is quite high, the instant claims are directed to a small subset of this area, amplified signal transduction pathways utilizing positive feedback loops. It is this area which is extraordinarily unpredictable, as is understood in the art as is evidenced by the reasonings discussed above and by Francis J. et al. as discussed above.

Applicants have provided a single working example of an amplified signal transduction pathways utilizing a positive feedback loop (FUS1-STE5). The different embodiments of the claims, as well as the parts of the specification referred to by Applicant, constitute merely an invitation to the highly skilled artisan to begin to try to find ways to get these embodiments to work. This amounts, simply, to a "wish to know" type invitation, and the amount of experimentation that would be required of the skilled artisan to answer such a wish would be unduly burdensome.

Applicant argues that there is nothing in the Francis et al. paper that conclusively establishes that Applicants' invention would not work in the system described in the Francis et al. paper. This argument has been fully considered but not deemed persuasive. Applicant is reminded that the assay system described by Francis et al. is encompassed by the broader claims of the instant application, e.g. claim 1. The assay system of Francis et al. does not work, as evidenced by the results set forth by Francis et al. and discussed above. Thus, one of ordinary skill in the art would appreciate that the Francis et al. paper does conclusively establish that this

particular embodiment of Applicant's invention does not work - contrary to Applicant's assertions.

Applicant argues that the specification has provided at least two working examples: Example 1 and 2; and that the examiner appears to require a working example of every embodiment. This argument has been fully considered but not deemed persuasive. First, it should be pointed out that Example 2 merely presents an invitation to determine if the invention works, see page 67: "The effects of these plasmids on signaling through the pheromone response pathway can be tested as for the STE5-expressing constructs described in Example 1". Thus there is no mention of any conditions that would be required to get the plasmids to work as claimed in the claims. Second, the examiner is not requiring any number of working embodiments. As discussed above, the examiner has indicated that the only working example provided in the specification (FUS1-STE5 construct) might be predicted to work in a positive feedback loop because it would not be expected to either cause constitutive activation of the response or diminished response due to the titration of rate limiting factors. Overexpession of STE5 is not known to cause high level constitutive activation of the mating response or to bypass the need for G-protein $\beta\gamma$ subunits (see page 1061 col. 1 of Hasson et al., Mol. Cell. Biol. 14(2)1054-1056, 1994, as discussed above). However, the level of unpredictability in these assay systems is quite high, as evidenced by the Francis et al. paper, and one could not predict the effects of other proteins in the assay system, particularly those that are known to cause constitutive activation of the cascade, e.g. STE4 overexpression results in constitutive activation

of the cascade (see page 105-1055 of Hasson et al., as discussed above) and would thus be expected to lead to constitutive activation of the cascade when its expression is controlled by the FUS1 promoter. Applicant does not appear to directly challenge these assertions.

Claim Rejections - 35 USC § 103

8. Claims 41, 43 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5691188 in view of Doi, K., et al. EMBO J. 13:1(61-70)1994.

Patent No: 5691188 teaches a recombinant yeast cell comprising a heterologous G-protein coupled receptor that, upon ligand stimulation, activates an endogenous yeast pheromone response pathway, wherein an endogenous yeast gene encoding a protein that negatively regulates the yeast pheromone system is mutated to render the protein nonfunctional such that signals generated by ligand binding to the receptor are amplified (see col 1 and 2, especially lines 23-36 of col. 2).

The claims require that the yeast gene encoding a protein that negatively regulates the yeast pheromone system be a phosphatase, specifically MSG5. U.S. Patent No: 5691188 does not specifically mention that the gene be a phosphatase, however 5691188 clearly teach that mutations in genes known to be involved in adaptation (desensitization) of the pheromone response are useful for further amplifying the signal (see lines 23-36 of col. 2). Doi, K., et al. EMBO J. 13:1(61-70)1994 teach that loss of msg5 function leads to diminished adaptive

response to pheromone (see the abstract). Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success to use yeast cells having a mutation in the msg5 gene as taught by Doi, K., et al. when practicing the invention of U.S. Patent No: 5691188. The motivation to do so was taught be U.S. Patent No: 5691188 wherein it was stated that mutations in genes involved in pheromone response desensitization are useful for practicing the invention, see lines 23-36 of col. 2.

Applicant argues that the 5691188 teaches only mutating genes directly participating in the yeast pheromone receptor kinase cascade. Applicant further agues that msg5 is a phosphatase and not a kinase and does not participate in the kinase cascade contemplated by the 5691188 patent, and that therefore an artisan would not be motivated to combine the references. This argument has been fully considered but not deemed persuasive. Applicant does not appear to understand the teachings of the 5691188 patent. Applicant is again referred to lines 23-36 of col. 2 of the 5691188 patent, wherein it is taught that mutations in genes known to cause desensitization of the pheromone response are useful for practicing the invention. The patent teaches that the products of these genes are known to modify the functions of the proteins that participate in the pheromone receptor transduction cascade, see line 27. Thus, in this passage, the patent teaches mutations in genes that modify the activities of the kinases that are part of the cascade, and not mutations in the kinases themselves, as applicant appears to assert. The patent lists several of these genes: SST2, STE50, AFR1 and SGV1; none of which are known to be part of the transduction cascade, and only one of which (SGV1) is a kinase.

Conclusion

Claim 51 is allowable.

Claims 1, 2, 4-9, 14-16, 23-40, 41, 43, 46-50 and 52

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

March 28, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600